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Patient and Care Delivery Characteristics Associated With Harm From Neuromuscular Blockade

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Objectives: To identify the prevalence of and evaluate factors associated with down-titration of sedation in patients receiving neuromuscular blockade.

Design: Retrospective cohort study.

Setting: Tertiary care teaching hospital in Boston, MA.

Patients: All patients over 18 years old admitted to the medical, surgical, or cardiac ICUs from 2013 to 2016, and who received cisatracurium for at least 24 hours.

Interventions: We examined patients for whom sedation was decreased despite accompanying ongoing neuromuscular blockade administration.

Measurements and Main Results: Of the 300 patients who met inclusion criteria (39% female, mean age of 57 yr old), 168 (56%) had sedation down-titrated while receiving neuromuscular blockade with a mean decrease in sedation dose of 18.7%. Factors associated with down-titration of sedation were bispectral index usage (90/168 [53.6%] vs 50/168 [29.8%] patients; $p < 0.01$; odds ratio, 1.82;

1.12–2.94), and bolus dose of neuromuscular blockade prior to continuous infusion (138/168 [82.1%] vs 79/168 [47.0%] patients; $p < 0.0001$).

Conclusions: Down-titration of sedation among mechanically ventilated patients receiving neuromuscular blockade was common and was correlated with bispectral index monitor usage. Clinicians should be aware of the limitations of quantitative electroencephalography monitoring devices and recognize their potential to cause inappropriate down-titration of sedation. Substantial opportunity exists to improve the quality of care of patients receiving neuromuscular blockade through development of guidelines and standardized care pathways.

Key Words: adult; critical care; deep sedation; neuromuscular blockade; patient harm; retrospective study

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Neuromuscular blocking agents (e.g., cisatracurium, rocuronium) are used in the ICU for patients with severe acute respiratory distress syndrome (ARDS), severe status asthmaticus, increased intracranial pressure, and patients undergoing targeted temperature management (1–3). The Reevaluation Of Systemic Early Neuromuscular Blockade (ROSE) trial found no mortality benefit with early use of neuromuscular blockade (NMB) in patients with ARDS (4, 5), although NMB still may be warranted for some patients with ARDS (6).

Many institutions have developed site-specific policies and employed a range of monitoring equipment for patients receiving NMB, and bispectral index (BIS) monitoring has been used for this purpose. BIS monitoring was initially employed for the monitoring of the level of sedation in patients under general anesthesia for surgical procedures. Some institutions have extrapolated it for use in the ICU to monitor sedation of mechanically ventilated patients, despite no evidence of clinical benefit in this setting (7, 8). Additionally, neither the ARDS et Curarisation Systematique (ACURASYS) nor the ROSE trial used BIS for

sedation monitoring, and neither trial allowed decreasing sedation after implementation of NMB (4, 5, 9). Using BIS for monitoring sedation in this setting may, in fact, be actively harmful to patients since prior work has shown that awareness can occur even with BIS values within the target range (10). Further, there is no way for providers to know that a patient remains adequately sedated after down-titration during NMB (11). Additionally, NMB use itself can change the BIS reading, which may actively contribute to the heterogeneity of care (11).

The purpose of this study was to identify the prevalence of patients who underwent down-titration of sedation despite receiving NMB and to identify factors associated with down-titration of sedation. We hypothesized that the use of available quantitative clinical monitoring devices, like the BIS monitor, was related to down-titration of sedation during NMB.

MATERIALS AND METHODS

Study Population and Data Source

We conducted a retrospective cohort study of adult patients hospitalized at a single tertiary academic medical center. Patients included were at least 18 years old, admitted to the medical ICU (MICU), surgical ICU (SICU), or cardiac ICU (CCU) from January 1, 2013, to December 31, 2016, and received cisatracurium for at least 24 hours. Demographic and clinical data of patients who fit the inclusion criteria were extracted from the electronic health record (EHR). Billing data was used to obtain the diagnosis-related group (DRG) as well as the comorbidities, assigned using methodology identified by Elixhauser (12). Patients in the neurosciences ICU were excluded from the study.

Patient Outcomes

The primary outcome of this study was down-titration of sedation while receiving NMB, defined as any decrease in dose of continuous sedative medications.

Patient and ICU-Level Variables

We reported patients' sex, age, race (white, black, and other), the 10 most common discharge diagnoses, type of ICUs (MICU, SICU, CCU), Sequential Organ Failure Assessment (SOFA) score at admission and on NMB administration (13), 10 most common Elixhauser comorbidities (12), predicted mortality by Elixhauser comorbidities, type of sedation (propofol, midazolam, dexmedetomidine), type of analgesia (fentanyl, hydromorphone, morphine), average days on ventilation, average days of NMB, time and day of the week of NMB order, the ratio of PaO₂ to FiO₂ (P/F) at time of NMB, pulse oximetry at time of NMB, and usage of the BIS monitor. Data were extracted from our institution's data repository of the EHR.

Statistical Analysis

All analyses were conducted using Statistical Analysis Software (SAS) 9.3 (SAS Institute, Cary, NC); the unit of analysis was ICU admission. None of the patients were readmitted to the ICU. We first described patient demographic and clinical characteristics in our cohort. Continuous data were represented using mean (\pm sd) and categorical data were presented using proportions. Next,

TABLE 1. Baseline Patient Characteristics (n = 300)

Characteristic	n (%)
Gender	
Female	116 (38.7)
Male	184 (61.3)
Age, mean \pm sd	57.1 \pm 15.9
Race	
White	181 (60.3)
Black	37 (12.3)
Other	18 (6.0)
Unknown	64 (21.3)
ICU	
Medical	158 (52.7)
Surgical	100 (33.3)
Cardiac	42 (14)
Sedation administered	
Propofol	145 (48.3)
Midazolam	206 (68.7)
Dexmedetomidine	1 (0.3)
Analgesia administered	
Fentanyl	274 (91.3)
Hydromorphone	13 (4.3)
Morphine	0 (0)
SOFA score at admission ^a , mean \pm sd	3.8 \pm 1.2
SOFA score at NMB administration ^a , mean \pm sd	4.0 \pm 1.2
Elixhauser comorbidities ^b	
Fluid and electrolyte disorders	142 (47.3)
Hypertension	111 (37.0)
Coagulation deficiency	70 (23.3)
Chronic pulmonary disease	48 (16.0)
Deficiency anemias	46 (15.3)
Diabetes	41 (13.7)
Depression	38 (12.7)
Congestive heart failure	38 (12.7)
Renal failure	37 (12.3)
Alcohol abuse	35 (11.7)
Elixhauser predicted mortality ^c , mean \pm sd	47% \pm 15
Days of NMB	2.0 \pm 2.7
Ventilator days	7 \pm 5.6

NMB = neuromuscular blockade, SOFA = Sequential Organ Failure Assessment. ^aScores range from 0 to 24, with higher scores suggesting higher mortality.

^bThe top 10 diagnosis-related groups and Elixhauser comorbidities were included.

^cElixhauser predicted mortality is based on Elixhauser comorbidities.

we conducted a bivariate analysis on whether BIS usage differed across patient and ICU characteristics. We also looked at the frequency of down-titration of sedation and whether it varied by patient, provider, and environmental characteristics. We used the chi-square test to test statistical significance on categorical variables and *t* test for continuous variables. Two-sided *p* values of less than 0.05 were considered statistically significant.

We fit a multivariable logistic regression to assess whether BIS usage, bolus of NMB, and the interaction between the two were associated with down-titration of sedation. The model was adjusted for BIS usage, bolus of NMB used, and the interaction between the two. The decrease in sedation dose was determined by taking the average decrease in sedation dose per patient during NMB and calculating the mean percent difference of those averages.

Our study was approved by the institutional review board at the Beth Israel Deaconess Medical Center with a waiver of informed consent.

RESULTS

A total of 300 consecutive patients met inclusion criteria for the study (Table 1). Thirty-nine percent of patients were female, with a mean age of 57 years. Patients were admitted most commonly with the DRG of severe sepsis with mechanical ventilation greater than 96 hours (10%), extracorporeal membrane oxygenation or tracheostomy with mechanical ventilation greater than 96 hours (9.7%), severe sepsis with mechanical ventilation less than 96 hours with major complication (8.7%), and respiratory system diagnosis with greater than 96 hours of ventilatory support (6.3%). The majority of patients were located in the MICU (52.7%), and most patients received midazolam for sedation (68.7%) and fentanyl for analgesia (91.3%). The most common Elixhauser comorbidities were fluid and electrolyte disorders (47.3%), chronic hypertension (37%), coagulation deficiency (23.3%), and chronic pulmonary disease (16%) (Table 1). The BIS monitor was used 75% of the time (*n* = 140), and those patients located in the MICU were

TABLE 2. Patient Characteristics Organized by Bispectral Index Monitor Usage

Characteristic	BIS Monitor Used, <i>n</i> (%)	No BIS Monitor, <i>n</i> (%)	<i>p</i>
Total	140 (46.7)	160 (53.3)	
Gender			
Female	53 (37.9)	63 (39.4)	0.78
Male	87 (62.1)	97 (60.6)	
Age, mean ± sd	56.3 ± 15.5	57.8 ± 16.2	0.41
Race			
White	76 (54.3)	105 (65.6)	0.22
Black	19 (13.6)	18 (11.3)	
Other	9 (6.4)	9 (5.6)	
Unknown	36 (25.7)	28 (17.5)	
ICU			
Medical	92 (65.7)	66 (41.3)	< 0.0001
Surgical	22 (15.7)	78 (48.8)	
Cardiac	26 (18.6)	16 (10.0)	
Sedation administered			
Propofol	74 (52.9)	71 (44.4)	0.14
Midazolam	101 (72.1)	105 (65.6)	0.22
Patients with documented Richmond Agitation-Sedation Scale prior to NMB	94 (67.1)	109 (68.1)	0.85
Ratio of Pao ₂ to Fio ₂ at NMB ^a , mean ± sd	171.3 ± 202	207.5 ± 163	0.10
Peripheral capillary oxygen saturation at NMB, mean ± sd	94.4 ± 6.6	94.3 ± 10.4	0.88
SOFA at admission ^b , mean ± sd	3.8 ± 1.2	3.8 ± 1.2	0.44
SOFA at NMB ^b , mean ± sd	3.9 ± 1.3	4.1 ± 1.2	0.24
Train of four monitor used	137 (97.8)	158 (98.7)	0.54

BIS = bispectral index, NMB = neuromuscular blockade, SOFA = Sequential Organ Failure Assessment.

^aA ratio less than 300 suggests acute respiratory distress syndrome with lower numbers suggesting greater severity.

^bScores range from 0 to 24, with higher scores suggesting higher mortality.

significantly more likely to have a BIS monitor than patients in the SICU (66%; $p < 0.001$) (Table 2).

Of the 300 patients, 168 (56%) had at least one sedating medication down-titrated while receiving NMB with a mean decrease in sedation dose of $18.7\% \pm 22.9\%$ (Table 3). The average mean arterial pressure (MAP) at the time of down-titration

of sedation was a mean of 76 ± 22 mm Hg. Factors associated with down-titration of sedation were BIS usage (54% vs 30% of patients; $p < 0.01$; odds ratio [OR], 1.82; 1.12–2.94), bolus dose of NMB prior to continuous infusion (82% vs 47% of patients; $p < 0.0001$; OR, 3.1; 1.8–5.2). Patients who had sedation down-titrated also had a lower mean SOFA at time of NMB

TABLE 3. Patient, Provider, and Environmental Characteristics by Down-Titration of Sedation

Characteristic	Sedation Down-Titrated, <i>n</i> (%)	No Sedation Down-Titrated, <i>n</i> (%)	<i>p</i>
Total	168 (56.0)	132 (44.0)	
Gender			
Female	61 (36.3)	55 (41.7)	0.34
Male	107 (63.7)	77 (58.3)	
Age, mean \pm SD	56.4 \pm 16.2	57.9 \pm 15.5	0.38
Race			
White	103 (61.3)	78 (59.1)	0.79
Black	21 (12.5)	16 (12.1)	
Other	8 (4.8)	10 (5.6)	
Unknown	36 (21.4)	28 (21.2)	
ICU			
Medical	91 (54.2)	67 (50.8)	0.75
Surgical	53 (32.5)	47 (35.6)	
Cardiac	24 (14.3)	18 (13.6)	
NMB order shift ^a			
Day ^b	59 (35.1)	46 (34.8)	0.96
Night ^c	109 (64.9)	86 (65.2)	
NMB ordered day			
Weekday	127 (75.6)	93 (70.5)	0.31
Weekend	41 (24.4)	39 (29.6)	
Number with documented Richmond Agitation-Sedation Scale prior to NMB ^a	110 (65.5)	93 (70.5)	0.36
Received bolus dose of NMB ^a	138 (82.1)	79 (59.9)	< 0.0001
Bispectral index monitor used	90 (53.6)	50 (37.9)	< 0.01
Train of four monitor used	167 (99.4)	128 (96.9)	0.1
Ratio of Pao ₂ to Fio ₂ at NMB ^{a,d} , mean \pm SD	208.7 \pm 216	165.9 \pm 118	0.03
Peripheral capillary oxygen saturation at NMB ^a , mean \pm SD	95.4 \pm 5.5	93.1 \pm 11.6	0.04
SOFA at admission ^e , mean \pm SD	3.7 \pm 0.9	3.9 \pm 1.4	0.34
SOFA at NMB ^e , mean \pm SD	3.8 \pm 1.0	4.3 \pm 1.4	< 0.0001
Elixhauser predicted mortality, mean \pm SD	47.1 % \pm 16.1	46.9 % \pm 13.6	0.93

NMB = neuromuscular blockade, SOFA = Sequential Organ Failure Assessment.

^aTime of NMB administration.

^bDay shift was defined as 07:00–18:59.

^cNight shift was defined as 19:00–06:59.

^dA ratio less than 300 suggests acute respiratory distress syndrome with lower numbers suggesting greater severity.

^eScores range from 0 to 24, with higher scores suggesting higher mortality.

(3.8 vs 4.3; $p < 0.0001$) and higher P/F at NMB (208.7 vs 165.9; $p 0.03$) (Table 3).

DISCUSSION

A substantial majority of critically ill patients at a tertiary care center receiving NMB had inappropriate reduction of their sedation, a reduction frequently associated with BIS monitor usage. It is generally accepted that doses of sedative medications should not decrease while patients are receiving NMB because both over-sedation and under-sedation in this setting have been associated with significant harm (1, 14, 15).

Our results show that reliance on quantitative clinical devices, like a BIS monitor, while patients are receiving NMB was associated with a high incidence of inappropriate sedation titration. Although we were unable to capture whether there was increased recall of NMB in these patients due to the retrospective nature of our study, we agree with published literature that down-titration of sedation during NMB in and of itself is generally inappropriate as providers are unable to accurately assess whether the patient remains adequately sedated. It is also important to note that, given the pharmacokinetics of NMB agents like cisatracurium, an initial bolus should be given when the NMB paralytics are first administered to ensure adequate drug levels of NMB until a steady state concentration is achieved (16). The fact that sedation was down-titrated in significantly more patients that received a bolus dose of NMB may further indicate inappropriate reliance on the BIS monitor to determine level of sedation as these patients are likely to achieve higher NMB faster. Further, as mentioned previously, NMB use itself can affect the BIS reading. Clinicians should therefore exercise caution in using the information from such devices to alter patient care in this setting. Additionally, the bolus of NMB may have contributed to hypotension, which may have prompted the clinician to down-titrate the dose of sedation. However, the average MAP of 76 mm Hg at time of down-titration of sedation argues against this as the sole reason for down-titration of sedation. Although there was a statistically significant difference between the SOFA score at initiation of NMB between patients in whom sedation was down-titrated versus those in whom it was not, the SOFA score difference of 0.4 is not clinically significant.

Based on the results of this study, our institution has since eliminated BIS usage for this indication. Further areas of study include review of down-titration of sedation since BIS monitor elimination to evaluate if the rates of down-titration have decreased.

There are several limitations with our study. First, our study was a single-center study of patients admitted to a large, urban academic medical center, which may not be easily generalizable to other institutions. Second, we used administrative data available in our EHR, which lacks the clinical nuance of a manual record review. Third, given the increasing volume of patients requiring critical care, MICU patients sometimes board in other ICUs in our institution. That is, a MICU team cares for a patient that is located in a different sub-specialty ICU. This may confound the lack of variability seen between ICUs.

CONCLUSIONS

Our findings illustrate that BIS monitor usage and administration of a bolus dose of NMB was associated with down-titration

of sedation in intubated patients receiving NMB in the ICU. Clinicians should be aware of the limitations of the BIS monitor and similar monitoring devices and use caution when using them to alter sedation management in the setting of NMB. Further areas for improvement in patient care involve reassessing sedation management after eliminating BIS usage at our institution and implementing a different measure to assess sedation in patients receiving NMB.

Although the ROSE trial did not show a mortality benefit to deep sedation and early NMB in all patients, NMB may still be used for select critically ill patients. It is important to ensure that these patients are cared for appropriately. Given that our institution had a relatively high usage of NMB compared with some other centers, these issues may extend to other institutions, and we would suggest a careful review of policies for appropriate sedation management during NMB.

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